

REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 1-33 and 35-37 are pending in the application. Claims 4-16, 19 and 23-36 have been withdrawn from consideration. Claims 1-3, 17, 18, 20-22 and 37 are under consideration and stand rejected.

By the present amendment, claims 1, 17, and 21 have been amended. Claim 1 has been amended to recite that the polypeptide comprises "at least one amino acid sequence of at most 20 and at least 7 consecutive amino acids defined in SEQ ID NO: 1" Support for the amendments to claim 1 can be found in the specification in at least page 2, first full paragraph. Claims 17 and 21 have been amended to delete recitations related to the former multiple dependencies of these claims. Support for claims 17 and 21 as amended can be found throughout the specification, for example in the claims as originally filed. No new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of this Amendment.

Restriction Requirement

The election with traverse of Group 25, comprising claims 1-3, 17-18, 20-22 and 37 has been made final. Claims 3 (parts a-e and g), 4-16, 19 and 23-36 have been withdrawn.

In view of the present amendment and the comments that follow, Applicants note that claims 1, 17-18, 20-22 and 37, as amended, continue to be generic to Groups 2-34. As no prior art of record anticipates or renders the elected species or the generic claims obvious, applicants respectfully request that the examination be expanded to encompass the entire genus described by claim 1 pursuant to M.P.E.P. § 809. Applicants reserve the right to petition the restriction requirement under 37 C.F.R. § 1.144.

Formal Matters

The Examiner has noted that the first sentence of the specification should refer to the provisional application to which priority is claimed. The Examiner's attention is respectfully directed to the first page of the application transmittal letter, submitted with the application on September 8, 2000, which includes the following request:

Please amend the specification by inserting before the first line the sentence --This application claims priority under 35 U.S.C. §§119(e) to Provisional Application No. 60/187,215 filed in the United States on March 3, 2000; the entire content of which is hereby incorporated by reference.--

If the foregoing amendment has not yet been entered, Applicants hereby renew the previous request. Accordingly, withdrawal of the objection is respectfully requested.

The specification is also objected to as containing embedded hyperlinks on page 29, because such links are potentially executable hypertext code. By the present amendment, the paragraph containing the hyperlinks has been amended to delete each occurrence of "http:\\\" and thereby convert potentially executable code into non-executable URL addressees. Accordingly, withdrawal of the objection is respectfully requested.

Information Disclosure Statement

Applicants understand that the documents marked A-1 to A-12 on the form PTO-1449 returned with the present Official Action that were submitted with the Information Disclosure Statement ("IDS") filed April 11, 2003 have not been found in the file by the present Examiner. Accordingly, replacement copies of these documents are submitted herewith. A new form PTO-1449 listing these documents is attached for the convenience of the Examiner. A copy of the stamped postcard showing receipt in the U.S. Patent and Trademark Office of 15 references with the IDS of April 11, 2003 is also attached. As the submission of these references was in compliance with the regulations when originally submitted, no further statement or fee is believed to be necessary. Accordingly, consideration of the documents and indication of such consideration on the form PTO-1449 is respectfully requested.

Drawings

Attached to the Official Action is a Notice of Draftsperson's Patent Drawing Review citing informalities in the numbering of view in Figure 12. Submitted herewith are formal drawings, which correct the cited informalities. Acceptance of the formal drawings and withdrawal of the objection are respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 17, 18, 21 and 22 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the following reasons:

Claim 17 stands rejected as allegedly indefinite for reciting "a vector comprising said polypeptide." Claim 17 has been amended to delete language relating to the former multiple dependancies of the claim. The metes and bounds of claim 17 as amended would hence be clear to one of skill in the art.

Claim 21 stands rejected for reciting "a vaccine comprising a polypeptide of," Claim 21 has been amended to delete language relating to the former multiple dependancies of the claim. The metes and bounds of claim 21, as amended, would hence be clear to one of skill in the art.

In view of the above, withdrawal of the rejection of claims 17, 18, 21 and 22 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 1-3, 17, 18, 20-22 and 37 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification for the full scope of the claims. This rejection is respectfully traversed.

Initially, it is noted that claims 1, 17, and 21 have been amended. Claims 2-3, 18, 20, 22 and 37 depend from certain of the amended claims. It is alleged in the Official Action that the claims encompass the genus "polypeptide amino acid sequences" and that this genus is not enabled by the specification. However, claim 1, as amended, recites a polypeptide comprising at least one amino acid sequence of at most 20 and at least 7 consecutive amino-acids defined in SEQ ID NO: 1, said polypeptide binding at least one MHC-I glycoprotein, with the proviso that said polypeptide is different from SEQ ID NO: 2. Thus, it is clear that the scope of the invention is polypeptides containing MHC-1 glycoprotein binding sequences of 7-20 sequential amino acids derived from SEQ ID NO: 1, but the polypeptide is not SEQ ID NO: 2. (The complete amino acid sequence defined by SEQ ID NO: 1, which is given in SEQ ID NO: 2, is specifically excluded.) The claimed genus is both sufficiently enabled and sufficiently described in the present specification.

Contrary to the assertions of the rejection, it is clear that the present claims are sufficiently enabled by the specification when considered in light of the teaching of the specification and the state of the art at the time the application was filed and analyzed under the reasoning of the Federal Circuit in *Wands*. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed.

Cir. 1988). Moreover, references cited as evidence in support of the rejection are not relevant to the present invention or do not support the rejection, thus the purported evidence fails to support a prima facie case of non-enablement. The Specification is enabling of the full scope of the invention, because the specification describes and enables a more than sufficient number of representative species of the claimed genus.

The Present Claims and Specification Satisfy the Enablement Test of *Wands*

The rejection purports to apply the factors set forth in *In re Wands*, 8 U.S.P.Q.2d 1400,1040 (Fed. Cir. 1988), to determine whether undue experimentation is required to practice the invention. However, in considering the question of enablement, one must consider the factors set forth in *Wands* in the context of the unambiguous reasoning and the resultant holding in *Wands*. It is respectfully submitted that applying the reasoning of the Federal Circuit in *Wands* to the present facts shows that the present claims are more than adequately enabled by the specification in this application.

The rejection appears to approach the question of enablement for the full scope of the invention by asking the question "How much experimentation would be required to make and test every single polypeptide within the scope of the claim?" Thus, the observation that a myriad of peptides is encompassed by the claims is a stated basis for rejection. The proper question is whether, given the teaching of the specification, the state of the art, and the expectations of the skilled practitioner, it would require undue experimentation to make and use any polypeptide within the scope of the invention. See,

e.g. *In re Wands*, 8 U.S.P.Q. 2d, 1400 (Fed. Cir. 1988); M.P.E.P. § 2164.08. While it might not be economically desirable to make and test every conceivable species of the invention, the guidance provided in the specification is more than sufficient to guide the skilled practitioner to make and use a vast number of species within the scope of the claim without undue experimentation.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *In re Wands* at 1404. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.*

The sufficiency of the present disclosure to support enablement of the present claims can be illustrated by the holding in *Wands*. In that case, the specification described a method for making high-affinity IgM antibodies against HBsAg and an example of a preferred hybridoma cell line. The PTO contended that this disclosure enabled only a method of using the antibodies made by the deposited example cell line. However, the Federal Circuit agreed with the applicants that the disclosure was enabling of an assay using any high affinity IgM antibodies against HBsAg. *Id.*; *see also*, U.S. Patent No. 4,879,219 at Claim 1.

The reasoning of the Federal Circuit is important to note as it sets forth an example of what must be considered an enabled invention. The court found that the specification

gave considerable guidance, provided working examples, and that the practitioners in the field understood that identifying antibodies required screening and were prepared to undertake such screening as was required. *In re Wands*, at 1406.

Applying the test evidenced in *Wands*, the present claims are clearly enabled by the specification. The present specification provides significant guidance on the selection of amino acid sequences. For example, at page 10, the specification provides guidance with respect to preferably conserved HLA binding motifs and allowable substitutions in analogues. The specification references teachings in the art, provides working examples of a screening method to identify suitable polypeptides within the claimed genus, and provides 33 exemplary amino acid sequences identified by such screening. See, for example, the Examples set forth in the present application. Synthesis or expression of a polypeptide with a chosen sequence is routine in the art; any requisite screening can be done using the methods taught in the specification or other art recognized methods. Thus, there is no reason to doubt that a polypeptide as claimed can be made and used as taught in the specification.

With respect to claims 21 and 22, the rejection alleges that the specification does not teach how to use a vaccine or provide evidence that is reasonably predictive that the claimed vaccine is effective in vivo. However, the Examiner's attention is directed to Example 6. In this Example, vaccines comprising polypeptides that had been identified according to the methods taught by the specification as described in claim 1 demonstrated a protective effect in an art accepted mouse model of tumor growth. Thus, one of skill in the

art is provided with guidance, a demonstration of how to make and use a vaccine as claimed, and its effectiveness in an art accepted model.

The rejection also appears to consider that the claims are invalid because some species within the scope of claim 1 might be inoperative. By virtue of the functional recitations, claim 1 does not embrace any non-operative embodiments. However, to the extent that the claims, absent the functional recitations, might embrace a non-operative embodiment, that is not a basis for finding the claims invalid. It is not a function of the claims to specifically exclude possible inoperative substances. *Atlas Power Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984).

Moreover, with respect to claims 21-22, directed to a vaccine composition, even if certain polypeptides described in claim 1 were not operative as a vaccine, the rejection has not provided any reason to doubt that the skilled practitioner in the vaccine art would know how to interpret routine preliminary screens of polypeptides that bind at least one MHC-I glycoprotein and to proceed with such further screening as may be necessary to identify functional vaccine compositions. That some experimentation is necessary does not preclude enablement. *Id.* at 413. The rejection has provided no evidence that such screening would be considered undue in the field. All tested compounds falling within the claim need not be optimal under all conditions for a valid patent. *Id.* Thus, under the reasonable standard set forth in *Wands* and *Atlas Powder*, the present claims are fully enabled by the guidance of the specification and working examples. The rejection has not

identified any circumstance that would require undue experimentation to practice the invention.

References Cited as Evidence in Support of the Rejection Are Not Relevant to Enablement of this Invention

Mere broad generalizations and allegations are insufficient for a holding of non-enablement. *See, e.g., Ex Parte Goeddel*, 5 U.S.P.Q.2d 1449, 1450 (Bd. Pat. App. & Int. 1987). Thus, it was not enough for the Examiner to allege non-enablement on the grounds that "protein chemistry is probably one of the most unpredictable areas of biotechnology." *See, Id.*

There is no evidence showing that the teaching of the specification is lacking in any specific way. References cited on pages 7-8 of the Official Action as evidence of non-enablement are not relevant to the enablement of the present invention. That two proteins, designated GIF and MIF, which are unrelated to the present invention, might differ in a single amino acid or that one position in a, likewise unrelated, transforming growth factor appears to have a significance in that protein's function has no bearing on the sufficiency of the present specification. The present specification relates to the identification and use of polypeptides comprising short linear epitope sequences and contains substantial guidance and working examples regarding appropriate selection of amino acid sequences.

On page 8, the Examiner refers to the issue of predictability in protein folding. There is no discussion of how this problem relates to polypeptides comprising one or more

short linear epitopes. The Examiner asserts, in a broad generalization, that minor structural differences can result in different biology, expression, or pharmacology of proteins. However, there is no evidence relating in particular to the relevant functional activity of binding to at least one MHC-I glycoprotein.

Contrary to the assertion of the rejection, to make a polypeptide following the teachings of the specification, one need only consider whether a selected sequence is consistent with the guidance of the specification and knowledge in the art regarding properties and requirements of MHC-I binding polypeptides. For example, one of skill in the art would be aware of the papers cited in the Official Action, Engelhard, *Curr. Opin. Immunol.* 6:13-23 (1994), and Guo et al., *Nature* 360:364-66 (1992). These papers evidence a certain level of such knowledge in the art at the time the application was filed. The skilled artisan must then only confirm, using methods provided in the specification or recognized in the art, that the chosen amino acid sequence binds to at least one MHC-I glycoprotein as recited in claim 1. The rejection provides no evidence to support any doubt that one of skill in the art could make and use the invention as claimed.

The specification is enabling for the full scope of the claimed invention, because a sufficient number of representative species are disclosed, together with explicit disclosure of additional members.

It is acknowledged in the Official Action that the specification is enabling for polypeptides consisting of SEQ ID NOS: 3-33 and 65-66, which are species of the genus

described in claim 1. Applicants submit that these 33 examples are sufficiently representative of the claimed genus. However, Applicants also note that myriad polypeptides representative of the species are disclosed and enabled in the specification by straightforward derivation from these examples and combinations thereof according to explicit instructions in the specification.

For example, a large number of further polypeptides representative of the genus can be derived from the 33 exemplary epitope sequences, for example, by simply including one or more additional sequential residues defined by SEQ ID NO: 1, totaling no more than 20 sequential residues at a stretch. In this regard, note that Engelhard, *Curr. Opin. Immunol.* 6:13-23 (1994), cited in the Official Action, teaches that contrary to earlier reports, longer peptides have been shown to bind with affinities comparable to those of predominant 8-mer and 9-mer sequences. (*See*, Engelhard at page 14, column 1.)

The number of representative species of the genus of claim 1 disclosed and enabled by the specification becomes astronomical when considering polypeptides, as taught in the specification, comprising combinations of epitope sequences. Applicants direct the Examiner's attention to, for example, pages 6-7 and 13-15, where the specification teaches that the polypeptide can contain one or more copies of one or more epitopes, possibly separated by linker sequences or protease cleavage sites. Linker sequences and protease cleavage sequences are known in the art. As further examples, the specification teaches that the polypeptide can also contain non-epitope sequences, such as adjuvant and targeting

sequences, and may be incorporated into fusion peptides comprising sequences from different proteins. (See, the specification at page 7.)

As a non-limiting illustration, the number of disclosed and enabled polypeptides comprising 1, 2, 3, 4 or 5 different epitopes chosen from among the 33 exemplary sequences has about 284,273 members, give or take a rounding error. The number of species taught by the specification is even more enormous considering variants derived by optionally including in the polypeptides one or more adjoining sequential residues from SEQ ID NO: 1 in one or more of the epitopic amino acid sequences and/or including different linker sequences or intervening protease cleavage sequences, and the like. Surely, that is a representative number of members of the claimed genus.

Applicants respectfully submit that the specification enables one of skill to make and use any polypeptide of the genus described by claim 1. Myriad representative examples can be derived from the explicit instructions in the specification. These examples must be considered together with the general guidance of the specification and knowledge of one of skill in the art. In view of the foregoing, the skilled practitioner can choose among the various features and combinations described in the specification in a polypeptide of the invention, possibly including other sequence elements recognized in the art to aid expression, processing, tagging, and purification without departing from the scope of the invention.

This is an appropriate use of the transitional phrase "comprising." "Comprising" is a term of art used in claim language which means that the named elements are essential,

but other elements may be added and still form a construct within the scope of the claim. *Genentech Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 U.S.P.Q.2d 1608, 1613 (Fed. Cir. 1997) (citing *In re Baxter*, 656 F.2d 679, 686, 210 U.S.P.Q. 795, 802 (C.C.P.A. 1981)). From the foregoing, it is clear that while claim 1 describes essential features of the polypeptide, additional features in various combinations and variations, as taught and enabled by the specification and/or recognized in the art, including simply additional sequence which does not interfere with the recited functional properties are enabled by the teaching of the specification taken with the skill in art.

For at least the foregoing reasons, Applicants respectfully submit that the rejection of claims 1-3, 17, 18, 20-22 and 37 under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification for the full scope of the claims is incorrect, and request its withdrawal.

Rejection under 35 U.S.C. § 112, first paragraph (Written Description)

Claims 1-3, 17, 18, 20-22 and 37 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Claims 1, 17, and 21 have been amended. To the extent that the rejection might be applied to the claims as amended, the rejection is respectfully traversed.

Claim 1, as amended, recites a polypeptide comprising at least one amino acid sequence of at most 20 and at least 7 consecutive amino-acids defined in SEQ ID NO: 1, said polypeptide binding at least one MHC-I glycoprotein, with the proviso that said polypeptide is different from SEQ ID NO: 2. Thus, it is clear that the scope of the subject matter relates to polypeptides containing MHC-I binding sequences derived from SEQ ID NO: 1, but the polypeptide is not SEQ ID NO: 2. (The complete sequence amino acid sequence defined by SEQ ID NO: 1, given in SEQ ID NO: 2, is specifically excluded.) This genus is more than sufficiently described in the present specification.

The rejection refers to *Fiers v. Revel*, 25 U.S.P.Q. 1601, 1606 (Fed. Cir. 1993), in asserting that the written description provided by the inventors is inadequate. However, upon consideration of the standard for written description that is illustrated in *Fiers*, it is clear that applicants have provided more than adequate description of the claimed genus.

In *Fiers*, the standard for written description is analogized to the standard for establishing conception. *Id.* at 1606. Conception is accomplished when one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, **or whatever characteristics sufficiently distinguish it.** *Id.* at 1604 (emphasis added). In *Fiers*, conception was held not supported by description limited to a protocol for isolating a gene and just a partial sequence of the gene. *Id.* at 1606-07. Thus, the written description requirement is not met where one has not described even one complete and functional member of the genus of the count. *Id.*

Contrary to the situation in *Fiers*, in this case, the specification provides explicit written description of many representative species of the claimed genus and defines the genus by distinguishing structural and chemical properties. The claimed genus is described by essential structural features, being a polypeptide comprising at least one amino acid sequence of at most 20 and at least 7 consecutive amino-acids defined in SEQ ID NO: 1. The genus is further defined by a chemical property related to the recited structural features which further defines the claimed genus, being a polypeptide binding at least one MHC-I glycoprotein.

As discussed above with regard to the enablement of the present claims, the specification describes a large number of representative species of the claimed genus. For example, polypeptides comprising one or more of the amino acid sequences defined by SEQ ID NOS: 3-33 and 65-66, optionally connected by linker sequences or protease cleavage sites and/or connected to other non-epitopic sequences. See pages 6-8 and 13-15. Protease cleavage sequences and other suitable linker sequences are known in the art. Use of known components, in a manner auxiliary to the invention must have a written description only so specific as to lead one of ordinary skill in the art to that class of material. A functional recitation of those compounds may be sufficient. *See In re Herschler*, 200 U.S.P.Q. 711, 714 (C.C.P.A. 1979).

Thus, the number of representative species of the genus of claim 1 that are disclosed and enabled by the specification is astronomical considering such polypeptides, described in the specification, comprising combinations of epitope sequences. As a non-

limiting illustration, the number of disclosed and enabled polypeptides comprising 1, 2, 3, 4 or 5 different epitopes chosen from among the 33 exemplary sequences has about 284,273 members, give or take a rounding error. Thus, the number of representative species described in the specification is more than sufficient to support the claimed invention.

In view of the at least the foregoing, the requirements of 35 U.S.C. § 112, first paragraph are met by the specification for all pending claims of the application. Accordingly, withdrawal of the rejection of claims 1-3, 17, 18, 20-22 and 37 under 35 U.S.C. § 112, first paragraph is appropriate and is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1, 17, 18, 20-22 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Van Baalen et al. (WO 98/17309) as evidenced by Rammensee et al. (*Immunogenetics*, 41:178-228, 1995). Without acceding to the rejection, claim 1 has been amended, claims 17, 18, 20-22 depend from claim 1. Van Baalen et al. does not anticipate or even suggest a polypeptide as described by claim 1 as amended. Accordingly, the rejection is traversed.

It is asserted that Van Baalen et al. disclose a 9 mer (SEQ ID NO: 19) that comprises 3 consecutive amino acids of SEQ ID NO: 1 that is 55.6% identical to SEQ ID NO:26. It is further asserted that Van Baalen et al. disclose a composition comprising the polypeptide and a vaccine comprising the polypeptide. It is further alleged that Rammensee

et al. evidences that the claimed polypeptide sequence inherently binds at least one MHC-I glycoprotein.

Van Baalen et al. does not disclose a polypeptide as described in claim 1. Claim 1, as amended, recites a polypeptide comprising at least one amino acid sequence of at most 20 and at least 7 consecutive amino-acids defined in SEQ ID NO: 1, said polypeptide binding at least one MHC-I glycoprotein, with the proviso that said polypeptide is different from SEQ ID NO: 2.

In view of the foregoing, withdrawal of the rejection of claims 1, 17, 18, 20-22 under 35 U.S.C. § 102 as allegedly anticipated by Van Baalen et al. is respectfully requested.

Claims 1-3, 17-18 and 20-22 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wreschner (WO 96/03502 A2) as evidenced by Rammensee et al. (supra). It is alleged that Wreschner discloses a polypeptide (noted in the Official Action as SEQ ID NO: 17 although this identifier was not found in the reference) that is 100% identical to elected species SEQ ID NO: 26. It is further alleged that Wreschner discloses compositions and vaccines comprising this polypeptide.

However, upon close examination of the sequence alignments provided with the Official Action, it is clear that the alignments show only small regions of larger MUC1 protein variants, shown in FIGS 6 (A-D) of the reference. Although the sequence of SEQ ID NO: 26 might be found within MUC1 proteins disclosed by Wreschner, it will be noted that all polypeptides taught by Wreschner are larger proteins or substantial fragments of

larger proteins. All such polypeptides of Wreschner have greater than twenty consecutive amino acid residues of SEQ ID NO: 1. At page 5, Wreschner refers to functional derivatives which may be fragments of the peptides, but the functions of Wreschner's proteins are as receptor proteins and activating ligands for said receptors in human breast cancer cells. Examples of polypeptides comprising such partial amino acid sequences according to Wreschner are shown on pages 6-8 of Wreschner. Wreschner does not teach or suggest any polypeptide comprising at least one amino acid sequence of at most 20 and at least 7 consecutive amino-acids defined in SEQ ID NO: 1 that would be a "functional derivative fragment" of the whole proteins. Therefore, Wreschner does not teach or suggest making a polypeptide comprising SEQ ID NO: 26, a polypeptide described by claim 1, or any composition or vaccine comprising such a polypeptide.

In view of the foregoing, it is clear that Wreschner does not anticipate claims 1, 17, 18, 20-22. Accordingly, withdrawal of the rejection of these claims under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 103

Claim 37 stands rejected under 35 U.S.C. § 103 as allegedly unpatentable over Wreschner (supra) or Van Baalen et al. (supra) in view of Zuk et al. (U.S. Patent No. 4,281,061). The rejection is traversed.

As acknowledged in the Official Action, neither Wreschner or Van Baalen et al. teach or suggest a kit comprising a polypeptide and an adjuvant. Further, as described

above, neither Wreschner or Van Baalen et al. teach or suggest a polypeptide as described in claim 1, as amended.

Zuk et al. does not teach or suggest a polypeptide as described in claim 1. Thus, even if Zuk et al. can be read as suggesting making a pharmaceutical kit, Zuk et al. fails to cure the deficiencies of Wreschner and Van Baalen et al. Therefore, because the references individually or in combination do not teach or suggest every element of the claimed invention, a prima facie case of obviousness has not been established.

Accordingly, withdrawal of the rejection is requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

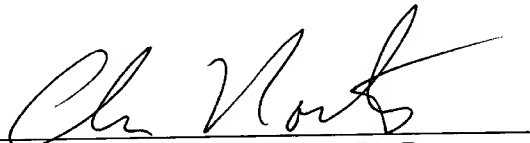
In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: September 2, 2003

By:



Christopher L. North, Ph.D.
Registration No. 50,433

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620